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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/349,194	07/07/1999	KENNETH F. BUECHLER	244/121	6285

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EXAMINER	
GABEL, GAILENE	
ART UNIT	PAPER NUMBER
1641	25

DATE MAILED: 03/07/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/349,194	Applicant(s) BUECHLER ET AL.	
	Examiner Gailene R. Gabel	Art Unit 1641	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *85-96,102-106 and 114-142* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *85-96,102-106 and 114-133* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Amendment Entry

1. Applicant's response filed 12/19/02 in Paper No. 23 is acknowledged and has been entered. Currently, claims 85-96, 102-106, and 114-142 are pending and are under examination.

Rejection Maintained

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

2. Claims 85-96, 102-106, and 114-133 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabled for an assay for determining free and complexed cardiac specific isoforms of troponin (cTn) using a cocktail of antibodies, each having specific binding for free cTnI, binary complex of cTn, and ternary complex of cTn, does not reasonably provide enablement for an assay for determining free and complexed cTn using an antibody, i.e. single antibody, having specific binding for each and all of free cTnI, binary complex of cTn, and ternary complex of cTn. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

As set forth in In re Wands, 858 F .2d 731, 8 USPQ2d 1400 (Fed. Cir. 1988), enablement requires that the specification teach those in the art to make and use the invention without undue experimentation. Factors to be considered in determining, whether a disclosure would require undue experimentation include 1) the nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the quantity of experimentation necessary, 7) the relative skill of those in the art, and 8) the breadth of the claims.

The nature of the invention- the invention is directed to a method for determining the presence or amount of all free and complexed isoforms of cTn using a cocktail of antibodies having specific binding for each and all of free, binary complex, and ternary complex isoforms of cTn.

The state of the prior art- the prior art of record fails to disclose a method for determining the presence or amount of all free, binary and ternary complexed isoforms of cTn using an antibody having specific binding for each and all of the free, binary, and ternary complexed isoforms of cTn.

The predictability or lack thereof in the art- there is no predictability based on the instant specification that the presence or amount of all of the free, binary and ternary complexed isoforms of cTn in a sample can be determined using an antibody wherein the antibody has specific binding for each and all of the free, binary, and ternary complexed isoforms of cTn.

The amount of direction or guidance present- appropriate guidance is provided by the specification for the claimed method to determine the presence or amount of all of the free, binary and ternary complexed isoforms of cTn in a sample using a cocktail of antibodies that have been generated to specifically bind one of the free, binary, and ternary complexed isoforms of cTn. However, the specification fails to provide any guidance to enable the claimed method to make and use an antibody that specifically binds all of the free, binary and ternary complexed isoforms of cTn in a sample to determine the total concentration of a cTn isoform.

The presence or absence of working examples- working examples are provided in the specification that show that all of free and complexed isoforms of cTn can be determined in a sample using a cocktail of antibodies that specifically bind each of the free, binary, and ternary complexed isoforms of cTn. There are no working examples that show analogous results using an antibody, which is encompassed by the broad scope of the instant claims.

The quantity of experimentation necessary- it would require undue amount of experimentation for the skilled artisan to make and use the method as claimed.

The relative skill of those in the art-the level of skill in the art is high.

The breadth of the claims- as recited, the instant claims are directed to a method that is capable of determining the presence or amount of all free, binary, and ternary complexed isoforms of cTn. As recited, the instant method is capable of determining the presence or amount of all of free, binary, and ternary complexed isoforms of cTn

using a single antibody that has specific binding for each of the free, binary, and ternary complexed isoforms of cTn.

In this case, the specification at pages 6-7 describes antibodies for use in the claimed method that are monoclonal, polyclonal, fragment thereof, and recombinant . These antibodies are characterized as being "sensitive" or "insensitive", the sensitive antibodies tend to bind and exhibit preferential detection of a single form of troponin and the insensitive antibodies tend to bind and exhibit detection of more than one form of troponin. In pages 13-14, the specification shows that an insensitive antibody is utilized to bind to the free and complexed forms of troponin; that is, insensitive with respect to the oxidized, reduced, and complexed forms of troponin. Alternatively, more than one sensitive antibody would be necessary to measure both the free and complexed forms of troponin. At pages 21-22, the specification shows how to generate and select antibodies that are sensitive or insensitive to the binding of free troponin I or T, troponin I or T in binary complexes, and troponin I or T in ternary I/T/C complexes; this is accomplished by purification of free troponin I or T, binary troponin I/T, T/C, and I/C complexes and ternary I/T/C complexes, respectively, then injection into mice or rabbits to generate monoclonal or polyclonal antibodies. The antibodies are then screened for affinity and specificity with the purified free troponin, binary complexes of troponin, and ternary complexes of troponin.

While the specification at pages 29-31 exemplifies using selected antibodies, i.e. a cocktail of antibodies, that bind each of free cTn, binary complexed cTn, and ternary complexed cTn, in the claimed method of determining the amount of free, binary

complexed, and ternary complexed cTn, the specification does not show any working examples of the claimed method using an antibody that has specific binding for all of the free cTn, binary complexed cTn, and ternary complexed cTn. The fact that insensitive antibodies that bind more than one form of cTn has been characterized, is not sufficient to enable the breadth of the claimed method to use a single insensitive antibody in an assay to determine the presence or amount of all of free cTn, binary complexed cTn, and ternary complexed cTn. The specification does not establish a direct correlation between using a cocktail of insensitive and/or sensitive antibodies and a single "insensitive" antibody, which would lead the skilled artisan to say that the claimed method works for a single insensitive antibody to enable the breadth of the claimed method. The specification does not provide any teaching that suggests that an antibody generated against purified free cTn, an antibody generated against purified binary complexed cTn, or an antibody generated against purified ternary complexed cTn, can be characterized to bind a conserved epitope for each and all of said free cTn, binary complexed cTn, and ternary complexed cTn in a sample. Further, the working examples at Example 15 and Example 16, also utilize a cocktail of antibodies to determine the presence or amount of all of free cTn, binary complexed cTn, and ternary complexed cTn in a sample. While it is not necessary to show working examples for every possible embodiment, there should be sufficient teachings in the specification that would suggest to the skilled artisan that the breadth of the claimed method is enabled. This is not the case in the instant specification. Thus, the claimed method is only

enabled for use with a cocktail of antibodies having binding specificity for each of free cTn, binary complexed cTn, and ternary complexed cTn.

In view of the teachings of In re Wands, 8 USPQ2d 1400, it has been determined that the level of experimentation required to enable the breadth of the claims is undue. It has been set forth above that 1) the experimentation required to enable the claimed method using a single antibody, would be great as 2) there is no experimental evidence provided that would indicate that the claimed method would work using a single insensitive antibody; 3) there is no proper guidance that shows that a single insensitive antibody has been generated, characterized, and selected to bind each and all of free cTn, binary complexed cTn and ternary complexed cTn, 4) the nature of the invention is a method capable of determining the presence or amount of all forms, i.e. free and complexed, of cTn using a cocktail of antibodies, 5) the relative skill of those in the art is high, yet 6) the state of the prior art has been shown to be unpredictable as evidenced by the fact that no prior art has been cited that shows generation, characterization, and selection of an antibody that has specific binding for each and all of free cTn, binary complexed cTn, and ternary complexed cTn , and lastly 7) the claims broadly recite a method for determining the presence or amount of all free and complexed forms of cTn using a single antibody that has specific binding for each and all of the free and complexed forms of cTn, without specifically stating how this can be done without undue experimentation.

Therefore, it is maintained that one of ordinary skill in the art could not make and use the invention as claimed without undue experimentation.

Response to Arguments and Declaration

3. Applicant's arguments filed 12/23/02 have been fully considered but they are not persuasive.

A) Applicant disagrees in Examiner's contention that there is no predictability based on the instant specification that the presence or amount of all of the free, binary, and ternary complexed isoforms of cTn can be determined using an antibody. Applicant, therefore, provided a declaration of Dr. Kenneth Buechler describing why those of ordinary skill in the art would readily acknowledge that the claimed antibody can be produced using only routine methods well known in the art. According to Applicant, such antibodies can have cardiac specific sites that remain available for antibody recognition and that can provide an epitope through which a single antibody can provide specific binding for each of all the free, binary, and ternary complexed isoforms. Applicant points to page 24, lines 21-29 to support their statement.

In response, page 24, lines 21-29 provides that the immunoassay can be formulated with specific antibodies that recognize epitopes of the troponin I and T in the complexes and also unbound troponin I and T. However, it does not provide that the immunoassay can be formulated with specific antibodies that recognize epitopes of troponin I and T in the unbound form and specifically both of the binary and the ternary form, which is encompassed by the scope of the rejected claims.

In response to Applicant's statement in the declaration provided by Dr. Kenneth Buechler describing that those of ordinary skill in the art would readily acknowledge that

the claimed antibody can be produced using only routine methods well known in the art, Applicant fails to provide evidentiary showing such as in the form of data, that supports generation, selection, and use of this antibody having conserved epitope that will bind each one of the unbound cTn, cTn in a binary complex form, and cTn in a ternary complex form in an assay. Likewise, nowhere in the specification provides equivalent support of the generation, selection, and use of an antibody having conserved epitope that will bind each one of the unbound cTn, cTn in a binary complex form, and cTn in a ternary complex form in an assay.

B) Applicant disagrees in Examiner's contention that the specification fails to provide guidance to enable the claimed method to make and use an antibody that specifically binds all of the free, binary, and ternary complexed forms. Applicant specifically argues that the specification describes methods for obtaining antibodies that are insensitive to the complex state of cardiac specific troponin isoforms, such as in page 21, line 3, through page 22, line 19.

In response, page 21, line 3 to page 22, line 19 provides generation and selection of antibodies that are preferentially either sensitive or insensitive to the binding of troponin I or T in binary complexes. It further provides generation and selection of antibodies that are preferentially either sensitive or insensitive to the binding of troponin I or T in ternary complexes. The antibodies are generated and selected by first screening for affinity and specificity with the purified binary or ternary complexes.

However, nowhere in the specification specifically shows of any generation and selection of an antibody having a conserved epitope that binds each one of the free, binary, and ternary complexed form of cTnI or cTnT, to encompass that the scope of the claimed invention.

C) Applicant disagrees in Examiner's contention that there are no working examples in the specification that show results using an antibody which is encompassed by the broad scope of the claims, i.e. antibody that binds each one of free, binary, and ternary complexes of cTn. Applicant points to Example 10 in the specification for a description of certain antibodies that are demonstrated to bind both of free and binary complexes of cTnI equally well. Applicant also notes that in the specification at page 62, lines 20-24, a skilled artisan would understand that the antibodies must bind both of free and binary complexes to form a sandwich assay. Applicant also points to Example 17 in the specification for a description of certain antibodies that are demonstrated to bind both of free and ternary forms of cTnT for use in a sandwich assay.

In response, Example 10 tests both monoclonal and polyclonal antibodies for their capacity to bind free cTnI and cTnI bound to cTnC in a binary complex, and found in page 63, lines 20-24 that some antibodies do bind free cTnI and binary complex forms of cTnI, equally well. Example 17 also tests both monoclonal and polyclonal antibodies for their capacity to bind free cTnT and cTnT bound to cTnC and cTnI in a ternary complex, and found that some antibodies do bind free cTnT and ternary

complex forms of cTnT, equally well. However, nowhere in Example 10 or Example 17 specifically provides any antibody generated and selected to bind any and all of free, binary, and ternary complexed forms of cTnI or cTnT, to encompass that the scope of the claimed invention.

D) Applicant disagrees in Examiner's contention that the quantity of experimentation necessary to produce and identify antibodies that are insensitive to the complexed state of cTn isoforms would be undue. Applicant further note in the declaration that methods for identifying antibodies that are insensitive to the complexed state of cTn isoforms are described in detail throughout the specification.

In response, the specification including all those noted and pointed out by Applicant in the arguments and declaration provide a description and use antibodies that are demonstrated to bind free and a binary form of cTn **or** free and a ternary form of cTn. However, nowhere in the specification provides or shows antibodies that are insensitive to each one of the unbound, binary, and ternary complexed states of cTnI, and which are generated and selected to bind all of free, binary, and ternary complexed form of cTnI or cTnT, to encompass that the scope of the claimed invention.

E) Applicant noted in item no. 9 of the declaration that the phrase "an antibody" recited in the claims would not be understood by the skilled artisan to imply a single molecule of antibody.

In response to Applicant's statement in the declaration, "an antibody", "a molecule", or "a cell" denotes a singular form of an element and does not necessarily imply a population, i.e. antibodies, molecules, cells. Alternatively, antibodies, molecules, or cells in a population are referred to as "antibodies", "molecules", or "a population of cells", set forth in a plural form, if so intended.

Allowable Subject Matter

4. Claims 134-142 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

5. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gailene R. Gabel whose telephone number is (703) 305-0807. The examiner can normally be reached on Monday to Thursday, 6:30 AM - 4:00 PM and alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Long Le can be reached on (703) 308-3399. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Christopher L. Chin

CHRISTOPHER L. CHIN
PRIMARY EXAMINER
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3/6/03

Gailene R. Gabel
Patent Examiner
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3/6/03